The Use of Carbamazepine in the Treatment of Schizophrenic and Schizoaffective Psychoses: A Review

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This article reviews current literature on the clinical efficacy of carbamazepine (CBZ) administration in schizophrenic and schizoaffective psychoses. With respect to the use of CBZ in cases of aggression, overactivity and other behavioral dyscontrol syndromes, only a few, mainly open, studies have been conducted. Attention to the efficacy of CBZ in schizophrenia and related psychoses was rather late in developing, with most of the studies done since 1981. Although the results of the different controlled and uncontrolled experiments are very difficult to compare, the results generally indicate beneficial effects — particularly if CBZ is used as an adjunct to neuroleptic medication. Suggestions for future research strategies to maximize the usefulness of CBZ in schizophrenia and related disorders are given.

Key Words: schizophrenia, schizoaffective psychoses, carbamazepine

INTRODUCTION

In the pharmacotherapeutic treatment of schizophrenia neuroleptics are frequently the first choice, even though these agents often work in an unsatisfactory way (Abbott and Loizon 1986; Davis 1980; Gardos and Cole 1976; Gerlach and Casey 1988; Johnson 1988; Thomas and McGuire 1986; Wisted and Palmsterna 1983). Neuroleptics are considered to be more effective in the treatment of positive symptoms and less efficacious with respect to negative symptoms (Eccleston et al 1985; Varga 1988; Angrist et al 1980). About 25% of patients diagnosed as schizophrenic are resistant to treatment or do not show sufficient improvement despite a regular neuroleptic dose regimen (Kane et al 1988) — an effect which may be related to dosage levels which are either too low or too high. Furthermore, there is another group of patients for whom initial treatment improvement is not sustained (Keith et al 1989; Hogarty et al 1977; Quitkin et al 1975; Lerner et al 1979; Lerner and Moscovich 1985).

Various strategies have been employed to maximize the effects of neuroleptics in the treatment of schizophrenia. One approach is to titrate dosage until a clinically therapeutic response is obtained (Lerner et al 1979; Bjorndal et al 1980; Hollister and Kim, 1977; Kane 1985). This strategy leads, however, to unwanted side effects (Gardos and Cole 1976; Johnson 1988; Kane and Smith 1982; De Zwaan and Schonbeck 1990). Another approach to optimize treatment has been to take plasma levels into consideration (Davis et al 1985; Dahl 1986; Aschauer et al 1988; Browne et al 1988; Meszaros et al 1990a; Cooper, 1978; Cooper et al 1976; Volavka and Cooper 1987; Baldessarini et al 1988). Many authors have stated that plasma level monitoring might be of clinical value, but there is still a lack of well-defined therapeutic and/or toxic ranges (Magliozzi et al 1981; Mavroidis et al 1983). The addition of lithium carbonate (Small et al 1975; Growe et al 1979; Alexander et al 1979; Carman et al 1981; Delva and Letemendia 1982; Zemlan et al 1984; Schulz et al 1989; Meszaros 1991) or propranolol (Atsmon et al 1972) to neuroleptics has been reported to be helpful, especially in patients with predominantly negative symptomatology. There are also reports dealing with the usefulness of benzodiazepines (Kahn et al 1988; Wolkowitz et al 1988; Csernansky et al 1988), amphetamines (van Kammen and Boronow 1988) and antidepressants (Müller 1981) in chronic schizophrenics with predominantly negative symptoms.

In the last decade the anticonvulsant carbamazepine (CBZ) has received increasing attention in the treatment of both neurological (Perenyi and Sztaniszlav 1985; Yassa

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1986; Krämer and Hopf 1987) and psychiatric disorders (Lerer 1985; Lerer et al 1985; Lerer et al 1987; Cookson 1987; Robertson 1987; Trimble, 1987a; 1987b; Elphick 1985; 1988; 1989a; 1989b; Müller-Oerlinghausen et al 1989; Schweizer et al 1991). Early studies involving the administration of CBZ reported positive psychotropic effects not only in psychotic patients with temporal lobe epilepsy (Pakesch 1963; Dehing 1968; Dalby 1971; Rodin et al 1974) but, later on, also in non-epileptic psychiatric disorders (Kuhn 1975; Kuhn-Gebhart 1975; Puente 1975; Bouvy et al 1988; Neppe 1988). More recently a relapse-preventing effect of CBZ in bipolar affective disorders (Ballenger and Post 1978; Okuma et al 1979; Ballenger and Post 1980; Nolen 1983; Robertson 1987; Prien and Gelenberg 1989; Simhandl et al 1990; Denk et al 1991), in mania (Okuma et al 1973; Okuma et al 1975; Okuma et al 1981; Cookson 1987; Lerer et al 1987; Okuma et al 1989) and in rapid cycling affective disorder (Post et al 1984; Schifano et al 1991) have been observed. Other studies have investigated the efficacy of CBZ in behavioral disorders characterized by aggression and overactivity (Monroe 1975; Dalby 1975; Tunks and Dermer 1977; Folks et al 1982; Cowdry and Gardner 1983; Cowdry et al 1983; Mattes et al 1984; Gardner and Cowdry 1986a; 1986b; Puente 1986; Post and Weiss 1987; Fichtner et al 1990).

UNCONTROLLED EXPERIMENTS AND CASE REPORTS

Table 1 summarizes important aspects of uncontrolled studies and case reports in which CBZ has been administered, and includes brief comments characterizing the main effects of this compound on symptomatology.

The uncontrolled studies listed in Table 1 differ along several important dimensions, including differences in diagnostic systems used, in heterogeneity of patient populations and pharmacological treatment, and in the duration of CBZ exposure. Despite these methodological differences, most of the studies reported decreases in aggressive or violent outbursts, and improvement in affective symptoms such as manic, dysphoric and, more rarely, depressive mood. In a few investigations, improvement of positive symptoms was observed.

CONTROLLED EXPERIMENTS

Table 2 presents a listing of controlled investigations in which CBZ was administered to patients with diagnoses of schizophrenia and schizoaffective disorder. Aspects of the study design and results will be presented below, followed by an integrative critical discussion.

Dehing (1968) reported positive "psychotropic effects of CBZ" when combined with neuroleptics in chronic schizophrenic patients (n = 13) characterized by EEG abnormalities. Improvement was observed in 6 patients showing what was termed an "epileptoid character defect."

De Vogelaer (1981) described positive effects of CBZ in 11 of 20 psychotic patients without EEG abnormalities diagnosed without reference to a conventional diagnostic system. Although patients were treated for only one week on CBZ or placebo, global ratings indicated that 11 patients were "better" on CBZ than on placebo, and 2 patients improved on placebo. The main symptoms showing improvement were Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) ratings of aggressiveness and paranoia. This experiment is the only one to report positive effects of CBZ after such a short treatment period.

In Neppe's study (1983) 13 patients received CBZ (average serum level: 25 Mol/l) or placebo added in combination with neuroleptics in a cross-over design. Patients were hospitalized and "predominantly chronic schizophrenics" with temporal lobe EEG abnormalities but without epileptic seizures. The sample consisted of 10 schizophrenics, 1 patient with a non-progressive alcohol dementia, 1 with a non-progressive posttraumatic dementia and 1 patient with a rapid cycling bipolar affective disorder. Diagnoses were made according to DSM-III criteria (American Psychiatric Association 1980). None of the patients was overtly hallucinatory. Two female schizophrenic patients dropped out, 1 eloped and the second developed CBZ hypersensitivity. Of the remaining 11 patients, 9 received neuroleptics in varying dosages and additional medication was administered as necessary. Patients were maintained on their same dosages of neuroleptics throughout the experiment. On an overall clinical rating, 9 patients showed more improvement after augmentation of CBZ than with placebo. One patient did not show any effect and another improved more on placebo than on CBZ. On the BPRS 8 patients improved more on CBZ than on placebo, 2 patients showed greater improvement on placebo, and 1 patient remained unchanged. Global assessments indicated greater improvement on CBZ than on placebo in 8 patients (4 markedly), while the clinical status of 3 receiving CBZ did not change. None of the patients improved more on placebo than on CBZ. The degree of improvement varied among patients in this experiment, with changes in symptomatology being significantly more pronounced when CBZ was administered in the second phase than in the first part of the study. Some subjects improved on CBZ to the point where they could be discharged, whereas others did not maintain the CBZ-associated improvements when switched to placebo. Improvements noticed included increases in self control in interpersonal situations and decreases in overt aggression.

Klein et al (1984) carried out the first double-blind, placebo controlled cross-over study of CBZ in acute, excited psychoses without EEG abnormalities. Twenty-three patients participated in the CBZ phase, 20 in the placebo phase and 10 in both phases. Research Diagnostic Criteria (RDC; Spitzer et al 1978) were utilized, but only patients with the diagnosis of an "excited psychosis" and prior failure to respond to neuroleptics and/or lithium treatment were included in the study. Before beginning CBZ administration CBZ (CBZ blood level: 8-12 mg/L), patients had been pretreated with haloperidol and also received other med-

Table 1

A summary of uncontrolled trials and case reports involving carbamazepine Administration

AUTHOR	MEDICATION	# OF PATS.	DIAGNOSIS	RESULTS	COMMENTS
Tunks & Dermer (1977)	CR CBZ	1	Aggressive behavior syndrome	+ 1	Aggression decreased
Stevens et al (1979)	CR CBZ, NL+CBZ	2	Schizophrenia EEG abnormal	0 1 CBZ -1 NL+CBZ	Temporal lobe epilepsy
Folks et al (1982)	OS CBZ, LI+CBZ	3 4 3	Schizoaffective Bipolar Organic affective synd.	+ 1 CBZ + 1 LI+CBZ + 1 CBZ	DMS III; EEG abnormalities; improvement in violent outbursts, depression, mania
Wunderlich et al (1982)	OS CBZ	21	Bipolars and schizoaffectives	+ 14	Improvement in schizophrenic symptoms, 12 weeks
Hakola & Laulumma (1982)	OS NL+CBZ	17 2	Schizophrenic Schizoaffective	+ 15	Clinical improvement, EEG abnormalities
Garbutt & Loosen (1983)	CR PB+CBZ	1	Schizophrenia	+ 1	Agitation reduced
Yassa & Dupont (1983)	CR CBZ	1	Schizophrenia	+ 1	Aggression reduced CBZ monotherapy
Brooks & Lessin (1983)	CR CBZ	1	Schizoaffective with diabetes insipidus	+ 1 CBZ	Improvement in dysphoria and depression
Ballenger & Post (1984)	CR, OS CBZ, NL+CBZ DPH+PB+CBZ	6	Schizophrenia	+ 4 CBZ + 1 HAL+CBZ + 1 CBZ	Positive and negative symptoms improved EEG abnormalities (4)
Luchins (1984)	CR,OS(A-B-A) NL+CBZ	6 1	I. Schizophrenia Mixed personality Disorder	+ 7	Aggression, verbal hostility reduced
	NL+CBZ	19	II. Hospitalized pts. (15 schizophrenia)	+ 19	Similar results EEG abnormalities (8)
Kraft et al (1984)	OS CBZ	1	Schizoaffective	+ 1	Hallucinations decreased markedly
Jenkins & Young (1984)	CR CBZ	1	Schizophrenia	+ 1	Clinical improvement
Elphick (1985)	OS CBZ, NL+CBZ NL+LI+CBZ	4 7	Schizoaffective Bipolar	+ 1 CBZ + 6	Overactivity, elation and sleep improved
McAllister (1985)	OS NL+CBZ	5	Organic brain diseases with atypical psychosis	+ 5	Affective liability decreased, EEG abnormalities
Jann et al (1985)	OS(A-B-A) HAL+CBZ	3	Schizophrenia	+ 2 0 1	Marked clinical improvement HAL plasma levels decreased
Kröber & Bisson (1985)	OS NL+CBZ	6	Schizoaffective	+ 5 0 1	Clinical improvement
Arana et al (1986)	OS HAL+CBZ	6 1	Schizophrenia Atypical psychosis	+ 1 - 3	HAL plasma levels decreased, GAS worsened
Wetterling (1987)	OS(A-B-A) CBZ,NL+CBZ	14	Schizophrenia	+ 4 NL+CBZ - 1 NL+CBZ	BPRS items excitement, tension, aggression improved
Rankel & Rankel (1988)	CR CBZ+HAL	1 1	Schizoaffective Schizophreniform	+ 2	Positive symptoms improved
Bouvy et al (1988)	CR CBZ	1	Posttraumatic organic brain syndrome, atypical psychosis	+ 1	Rapid clinical improvement
Yatham & McHale (1988)	CR CBZ	1	Aggressive behavior syndrome	+ 1	Aggression improved EEG abnormalities
Okuma et al (1989)	OS CBZ,NL+CBZ, NL+LI+CBZ, LI+CBZ	103 54 26	Affective psychoses Schizophrenia Schizoaffective	+ 75 + 30 + 16	Schizophrenic symptoms related to affect and emotion improved under CBZ; 15 drop outs
Kessler et al (1989)	OS CBZ,CBZ+LI	3	Organic delusional disorder with affective or schizophrenic symptoms	+ 3 CBZ	Positive, affective symptoms and obsessive thoughts improved
Fichtner et al (1990)	OS NL+CBZ	1	Multiple personality disorder	+ 1	Dissociation, affective symptoms improved; EEG abnormalities
Pupeschi et al (1991)	OS HAL+CBZ	21	Atypical psychoses	- 3	HAL plasma levels decreased

Design: **CR** — Case Report, **OS** — Open Study
Medication: **CBZ** — Carbamazepine, **NL** — Neuroleptic, **HAL** — Haloperidol, **LI** — Lithium Carbonate
Results: "-" Deterioration, "+" Improvement, "0" No Change

Table 2
A summary of controlled investigations involving carbamazepine administration

AUTHOR	MEDICATION	# OF PATS.	DIAGNOSIS	RESULTS	COMMENTS
Dehing (1968)	SB NL+CBZ/PLC	13	Schizophrenia	+ (6) CBZ	Epileptoid character defect, EEG abnormalities
De Vogelaer (1981)	DB, CRO NL+CBZ/PLC	20	Schizophrenia	+ (11) CBZ + (2) PLC	Aggression, paranoia in BPRS better, 1 week
Neppe (1983)	DB, CRO NL+CBZ/PLC	10 3	Schizophrenia Others	+ (8) CBZ + (2) PLC 0 (1) CBZ	Aggression, self-control, EEG abnormalities, 2 dropped out
Klein et al (1984)	DB, CRO HAL+CBZ/PLC	43	Atypical psychosis	CBZ > PLC	15/18 BPRS items improved 14 dropped out
Kamisada et al (1985)	DB NL+CBZ/LI	19	Atypical psychosis	CBZ = LI	Equal outcome
Kidron et al (1985)	DB HAL+CBZ/PLC	11	Schizophrenia	0 (4) CBZ 0 (5) PLC	10 weeks, BPRS no significant change
Gardner & Cowdry (1986b)	DB, CRO CBZ/PLC	16	Borderline personality disorder	+ (10) CBZ - (1) CBZ - (7) PLC	Behavior dyscontrol reduced, 6 weeks, 3 dropped out during PLC phase
Placidi et al (1986)	DB NL+AD+BD+CBZ/LI	83 56	I. Various psychosis II. Various psychosis	CBZ = LI CBZ = LI	Thought disturbances, activation, anergia better; 2 months, 27 drop outs, up to 3 yrs. follow-up, 25 drop outs
Dose et al (1987)	DB HAL+CBZ/PLC	22	Atypical psychosis	CBZ = PLC	BPRS, IMPS, EPS improved, 5 weeks, CBZ: less NL needed
Herrera et al (1987a)	SB (A-B-A) NL+CBZ	6	Schizophrenia	+ (6)	BPRS: anxiety, depression, emotional withdrawal better
Sramek et al (1988)	SB CBZ	13	Schizophrenia	+ (4) CBZ - (1) CBZ	BPRS total score, anxiety, depression better, 1 drop out
Schulz et al (1989)	DB I HAL II HAL+CBZ/LI	61 14	I. Atypical psychosis II. Nonresponders	+ (5/8) LI + (2/6) CBZ + (1/6) CBZ	BPRS total score, thought disorder better, 2 weeks
Mair et al (1990)	OS NL,NL+CBZ	40	Atypical psychosis	NL=NL+CBZ	13 entered CBZ phase for 30 days
Meszaros et al (1991c)	DB NL+CBZ/PLC	24	Schizophrenia	CBZ = PLC CBZ > PLC	In BPRS total score equal, BPRS and SANS subscores improved; 8 weeks
Kunovac et al (1991)	DB NL+CBZ/PLC	20	Schizophrenia	CBZ = PLC CBZ > PLC	BPRS total score equal, SANS subscores improved
Carpenter et al (1991)	DB, CRO HAL+CBZ/PLC	34 20	I. Schizophrenia II. Schizophrenia	CBZ = PLC CBZ = PLC	High relapse rate in both groups Complicate design

Design: **OS** — Open Study, **CRO** — Crossover, **DB** — Double Blind, **SB** — Single Blind
Medication: **CBZ** — Carbamazepine, **NL** — Neuroleptic, **HAL** — Haloperidol, **LI** — Lithium Carbonate, **PLC** — Placebo
Rating scales: **EPS** — Extrapyramidal Symptom Scale (Simpson and Angus 1970), **BPRS** — Brief Psychiatric Rating Scale (Overall and Gorham 1962), **IMPS** — Inpatient Multidimensional Psychiatric Scale (Lorr et al 1962), **SANS** — Scale for the Assessment of Negative Symptoms (Andreasen 1981)
Results: "-" — Deterioration, "+" — Improvement, "0" — No Change, "=" — Equal, ">" — Better, "()" — Number of patients with a change in special symptoms on subscores of rating scales

ication according to clinical need. Patients dropped out for reasons of depression (n = 3), remission of excited psychotic symptoms shortly after the beginning of the study (n = 3), uncooperativeness and negativism (n = 2), discharge against medical advice (n = 1), and drug discontinuation because of severe rash (n = 1). CBZ side effects noted included drowsiness, dizziness, diplopia, gait disturbances, nausea, vomiting, hypotonia and rash. Patients showing poor improvement at the end of the first phase of the study or who were readmitted to hospital a second time within the year of the study were considered for the cross-over study. Of 14 such patients, four did not participate because of unmanageable behavior, severe depression, completion of the first part of the experiment at the end of the first year study. The final data analysis was therefore conducted on 33 subjects. Both groups improved, with the CBZ group showing a more rapid improvement beginning during the third week. The degree of improvement of the CBZ-treated group was greater than that of the placebo group as reflected in change scores. However, group differences in improvement on the Clinical Global Impression Scale (CGI; Guy and Bonato 1976) did not reach statistical significance. The CBZ group showed improvement on 15 of 18 BPRS items (CBZ effects were measured by percentage of improvement over baseline

BPRS scores). Patients showed improvement in affective (excitement, tension) and schizophrenic symptoms (unusual thought content). All patients of the cross-over group showed a good response to CBZ beginning the third week of the experiment.

Kamisada et al (1985) compared the effects of either CBZ or lithium in conjunction with neuroleptics in 19 excited schizophrenic patients over 8 weeks. No differences in treatment outcome were reported between the CBZ and the lithium treated groups.

Kidron et al (1985) added CBZ to haloperidol treatment in 11 patients. All were hospitalized and had been diagnosed as chronic schizophrenics with significant positive symptoms (RDC criteria) and were without EEG abnormalities. Two patients did not complete the study (1 suicide, 1 self-discharge). All patients were maintained on a dose of haloperidol for at least 2 weeks before the experiment (average daily dose: 30 mg/day) and additional medication was administered as necessary. The dosage of haloperidol was unchanged throughout the 10 weeks of the study. CBZ or placebo was added to haloperidol and the therapeutic level of CBZ was reached within 14 days and continued for 5 weeks. CBZ and placebo were then switched and patients were treated for another 5 weeks. Between the 2 phases there was no wash out period. Neither the BPRS total score nor the subscores showed significant changes during the treatment with CBZ (baseline: 37, sd +/- 5; after 5 weeks: 34, sd +/- 10) compared to the placebo group (baseline: 39, sd +/- 10; after 5 weeks: 34, sd +/- 8). CBZ blood levels ranged between 5 - 18 μg/ml (average: 11.5 μg/ml). Relative to placebo, no patient on CBZ improved sufficiently to consider continuing treatment with CBZ. The fact that the CBZ treated group needed less neuroleptics was a notable feature of this study. Haloperidol plasma levels decreased significantly after supplementation with CBZ. No benefits were observed in patients with higher blood levels of CBZ.

Gardner and Cowdry (1986b) investigated the efficacy of CBZ vs placebo in 16 female patients, diagnosed as cases of borderline personality disorder with behavioral dyscontrol (according to DSM III and Gunderson's Diagnostic Interview for Borderline Patients; Gunderson et al 1981). The complete study involved cross-over experiments with placebo and four other compounds (CBZ, alprazolam, trifluoperazine and tranylcypromine). CBZ serum blood level was 8 - 12 μg/ml. The experiment consisted of a 2 week dose adjustment period, a 4 week steady dose administration period, and a 1 week medication free period before the next drug experiment. Two patients were excluded because of seizures, and three others left the study during the placebo phase but they finished the CBZ trial. Consequently, 11 CBZ/placebo experiments were included in the data analysis. Seven of the placebo experiments were discontinued because of clinical worsening, compared to only 1 such instance in the CBZ group. Two patients in the CBZ-treated group showed allergic reactions, and 1 CBZ experiment was discontinued because of reasons not related to the experiment. Ten CBZ patients showed less behavioral dyscontrol (including cuts in wrist, arms or abdomen, episodes of self-burning, episodes of violence and recurrent rage episodes).

Placidi et al (1986) investigated the usefulness of CBZ compared to lithium carbonate in acute and prophylactic (relapse defined as a CGI severity of illness score above 5) treatment of affective, schizoaffective and schizophreniform disorders. Patients were diagnosed according to DSM III criteria. Eighty-three inpatients and outpatients were randomly assigned to the treatment group (CBZ: 42 patients; lithium: 41 patients). Included in the CBZ group were patients who showed symptomatology with schizophrenic features (n = 11), rapid cycling bipolar disorder (n = 4), lithium nonresponding (n = 13) and incapacity or marked social declining (n = 38). Similarly, in the lithium group were patients with schizophrenic features (n = 18), rapid cycling (n = 4), nonresponding to lithium (n = 5) and social declining (n = 36). None of the patients had EEG abnormalities. Thirty patients (CBZ group: 17, lithium group: 13) had been pretreated with lithium before entering the experiment. Thirty-six CBZ patients and 30 lithium patients entered the experiment during an acute episode. A variety of assessment instruments were used, including the Adult Data Personality Inventory (Guy 1976), the Prior Medication Record (Guy and Bonato 1976), the CGI, the BPRS, the Dosage Record and Treatment Emergent Symptoms Scale (Guy and Bonato 1976), the Tess Write In Scale (Guy and Bonato 1976) and the Patient Termination Record (Guy and Bonato 1976). Nearly all patients received additional medication. CBZ (serum level: 7 - 12 mg/L) or lithium (serum level: 0.6 - 1.0 mEqu/L) was administered on a fixed flexible dosage schedule. Twenty-seven patients (13 CBZ and 14 lithium treated patients) interrupted the treatment during the first 2 months (acute treatment phase). A few patients discontinued because of side effects (drowsiness, diarrhea, elevated liver enzymes). A significantly higher number of drop outs occurred in the lithium treated group in patients with schizophrenic features. Twelve CBZ patients and 13 lithium treated patients dropped out during the maintenance phase. On the CGI, 2/3 of the patients of the CBZ and lithium groups improved during a 36 month period. According to the CGI "severity of illness" item, CBZ and lithium appeared to be equipotent in attenuating patients' symptomatology (observation period of 12 months). Both drugs seemed to exert the maximal effects during the first 3 months, but improvement was maintained throughout the following months. On the BPRS, both drugs were associated with improvement on "thought disturbances," "activation," "anergia," and "hostile suspiciousness" items. Twelve relapses in 8 patients of the CBZ group and 9 relapses in 7 patients of the lithium group were observed. The incidence of side effects was similar for both drugs. The large number of drop outs and the heterogeneity of diagnoses did not permit a clear conclusion concerning the efficacy of CBZ or lithium carbonate in schizophrenic patients.

Dose et al (1987) reported on the efficacy of CBZ added to low doses of haloperidol in 22 acute schizophrenic patients without EEG abnormalities. Patients had been diagnosed according to criteria of International Classification of Mental

Disorders (ICD- 9; World Health Organization 1978) and DSM-III as acute schizophrenics [paranoid (n = 15), catatonic (n = 1), acute psychotic (n = 1), simplex (n = 1), residual type (n = 1) and schizoaffectives (n = 3)]. The study lasted 5 weeks and patients received concurrent medication if necessary. By day 28 the CBZ treated group (n = 11) showed a 52% decrease in the average initial total BPRS score (initial: 2.9, sd +/- 0.5; day 28: 1.4, sd +/- 0.3). The total BPRS score increased (2.0; sd +/- 0.7) within 1 week after the discontinuation of CBZ. The placebo treated group (n = 11) also showed a decrease (43%) in the average initial total BPRS score (3.6; sd +/- 0.8; day 28: 2.0, sd +/- 0.7). On the Inpatient Multidimensional Psychiatric Scale (IMPS; Lorr et al 1962), the initial average total score (23.6, sd +/- 6.6) of the CBZ group decreased by 66% (8.0, sd +/ - 4.6) within 4 weeks and increased to 14.0 (sd +/- 6.9) within 1 week of CBZ discontinuation. The placebo-treated group showed a 60% decrease in the average initial total IMPS score [(30.1, sd +/- 10.4) to (12.0, sd +/- 7.2)] within the 4 week period, and only a mild increase after discontinuation of placebo for 1 week. One of the most remarkable features of this study is the fact that the CBZ treated group needed less neuroleptics [74% of the average haloperidol ($p < .05$) and 36% of the average chloprothixene dosage ($p < .05$)], less anticholinergics [28% of the average biperiden dosage ($p < .01$)] and experienced fewer drug side effects [39% of the average side effects ($p < .01$)] compared to the placebo group. The drug side effects were measured using the Extrapyramidal Symptom Scale (EPS) of Simpson and Angus (1970). There was a deterioration and increase of extrapyramidal side effects in the CBZ-treated group after discontinuation of CBZ. The authors concluded that the possibility of decreasing neuroleptic and anticholinergic dosage with the addition of CBZ might be helpful in avoiding neuroleptic side effects, and therefore the combined treatment of neuroleptic and CBZ might be a reasonable therapeutic strategy for some schizophrenic patients.

In a 10-week-study, Herrera et al (1987a) tested the efficacy of CBZ in combination with neuroleptics in 6 chronic nonresponsive schizophrenics (DSM-III) without EEG abnormalities. Treatment resistance was determined by the following criteria: treatment with at least 3 neuroleptics from 2 different chemical classes for a minimum of 6 weeks at a minimum dose equivalent to 1000 mg/ day of chlorpromazine during the previous 5 years, and failure to respond adequately to antipsychotic therapy during this time. CBZ was added to fixed dosages of neuroleptics (average neuroleptic dosage in chlorpromazine equivalent was 1980 mg/day; CBZ blood level: 6 - 12 μg/ml). The study included a two week evaluation period, six weeks of CBZ administration, and a two week wash out phase of the experimental drug to baseline medication levels. Clinical assessment was done using the BPRS. The ratings were completed by two psychologists blind to the procedures of the experiment. Patients showed improvement in depression, anxiety and emotional withdrawal subscores of the BPRS. All patients reported less sadness, despondency and anxiety. Also, positive symptoms, such as thought disturbances, were reduced.

Sramek et al (1988) described the efficacy of CBZ monotherapy in 13 male chronic schizophrenics diagnosed according to DSM-III criteria. The determination of treatment resistance was based on special criteria (see Herrera et al 1987a). Abrupt discontinuation of neuroleptics was followed by a 1 week wash-out period. Subsequently, only CBZ was administered for 5 weeks (therapeutic CBZ plasma level: 6 - 12 mg/ml). As concurrent medication, chloralhydrate was allowed. A psychiatrist and a psychologist blind to the procedure rated the patients. Twelve patients completed the experiment (1 dropped out because of increasing psychosis after the first week of CBZ treatment). Four patients significantly improved in BPRS total score and in the BPRS anxiety/depression subscores. Of these patients, 1 was discharged from hospital.

In a two phase study, Schulz et al (1989) investigated the efficacy of CBZ vs. lithium carbonate in schizophrenic nonresponders. In phase I, schizophrenic and schizoaffective patients (n = 61; DSM-III criteria) received treatment with haloperidol for 4 weeks. Clinical assessment (24 item BPRS of Bigelow and Murphey [unpublished]; Global Rating Scales) and haloperidol serum level measurements were done weekly (dosage adjusted to maintain levels between 8 and 25 μg/ml). Forty-four patients completed this 4 week experiment. Phase II subjects were 17 nonresponders with total BPRS scores above 40 and in whom positive symptoms had also been identified. Of this group, 14 patients received either CBZ (n = 6; therapeutic level: 8 - 12 mg/ml) or lithium carbonate (n = 8; therapeutic level: 0.6 - 1.0 mEqu/l) augmented with haloperidol for two weeks. Benztropine and benzodiazepines were allowed if necessary. Nonresponders showed higher scores of neurological soft signs and lower scores on the Mini Mental State Examination (Folstein et al 1975). In the CBZ treated group two patients showed improvement in BPRS total scores (53.8 to 46.7) and in BPRS thought disorder subscores (13.2 to 10.8). Five patients of the lithium group improved in BPRS total score (58.8 to 41.1) and in BPRS thought disorder subscores (11.6 to 7.6). The remaining 7 nonresponding patients had been ill for a shorter time, had higher Mini Mental scores on admission and a positive family history of schizophrenia. Haloperidol serum levels and the level-to-dose ratios dropped about 50% after receiving CBZ; haloperidol levels remained unchanged in the lithium group. The clinical status of one patient receiving CBZ worsened in association with a drop in haloperidol serum level, whereas two others showed a significant symptom reduction despite a drop in the haloperidol serum level.

Mair et al (1990) studied the efficacy of haloperidol and clozapine in acute female schizophrenic patients (n = 40). If patients did not respond to neuroleptic treatment after 5 days, CBZ (600 mg/day) was added. Only patients with a total BPRS score above 30 and a minimum CGI score of 4 were included in the study. The initial dose of haloperidol was 25 - 50 mg/day, and the initial dose of clozapine 300

mg/day. Concurrent medication was allowed if necessary. Seven patients in the haloperidol group and six in the clozapine group received CBZ. All 4 groups (haloperidol + CBZ, haloperidol, clozapine + CBZ, clozapine) were observed for 35 days. Only the haloperidol+CBZ treated group showed a significant improvement between days 5 and 21. Although all other treatment groups showed clinical improvement, the amount of improvement was not statistically significant. The haloperidol+CBZ treated group developed more extrapyramidal side effects than the haloperidol-only group (but patients required a higher dosage of haloperidol between days 10 and 21). On the basis of these results, the authors concluded that combined neuroleptic and CBZ therapy does not improve the efficacy of a pure standard neuroleptic medication.

Meszaros et al (1991c) evaluated the therapeutic effects of CBZ in 24 chronic schizophrenic patients (DSM-III-R criteria) without EEG abnormalities (2 disorganized, 3 paranoid, 14 residual and 5 undifferentiated types). Only patients who had not responded to at least three neuroleptics from two different chemical classes during the last two years, and who had a fixed long acting and/or oral neuroleptic medication within the last 4 weeks before starting the experiment were included. Either CBZ or placebo was administered with neuroleptics for a 6 week period and was followed by a 2 week placebo period. Improvements were observed in both groups on the BPRS anxiety/depression, the anergia — and the thought disturbance subscales, and in the affective flattening, attention, abulia, anhedonia and alogia item of the Scale for the Assessment of Negative Symptoms (SANS; Andreason 1981). On several subscales improvements in the CBZ group were statistically significant in comparison to the placebo group. Further assessments were done using the AMDP Rating ("Arbeitsgemeinschaft fur Methodik und Dokumentation in der Psychiatrie" 1979). On this scale patients in both groups again showed improvement on positive and negative items. The Tardive Dyskinesia Scale (Simpson et al 1979) and the Rating Scale for Extrapyramidal Side Effects (Simpson and Angus 1970) showed improvement for both groups but no significant differences between groups. In summary, both groups showed improvement and there were significant improvements in both positive and negative symptoms under CBZ compared to placebo.

Kunovac et al (1991) evaluated the therapeutic effects of CBZ in 20 chronic schizophrenic patients (DSM-III-R criteria). Other assessments [BPRS, HAMD (Hamilton 1960), SANS] were done at admission and at week 6. Patients receiving neuroleptics were randomized into CBZ and placebo groups. The authors concluded that "CBZ should have a place as an adjuvant therapy in the treatment of schizophrenia."

Carpenter et al (1991) evaluated the efficacy of CBZ maintenance treatment in chronic non-manic schizophrenic outpatients (RDC and DSM III criteria) using a cross-over design. Patients were pretreated with neuroleptics, and all were in a stabilized condition. Prior to each phase patients received either CBZ or placebo on a double-blind basis in addition to their neuroleptics. The dosage of the study medication was increased to a maximum of 4 tablets over a period of 12 days. After attaining the maximum dosage of CBZ, neuroleptics were withdrawn and patients received 4 to 6 tablets of study medication (CBZ: 800 - 1200 mg/day). The concurrent medication allowed was chloral hydrate and diphenhydramine hydrochloride during neuroleptic withdrawal. Assessments (BPRS, Monroe Scale; Pluchik et al 1976) and the taking of blood samplings were done weekly. The criteria for treatment effectiveness included the number of relapses and the time to relapse within a 95 day neuroleptic free period (relapses determined by ratings and clinical judgments). Twenty-seven patients (18 male, 9 female) diagnosed as paranoid (n = 14), undifferentiated (n = 10) and disorganized (n = 3) types finished this initial part of the study. There was no significant difference between treatments in the proportion of patients relapsing (13/13 CBZ group, 11/14 placebo group). Independently from medication, high total scores on the Monroe Scale were associated with early relapse. The differences in relapse duration between the high and low Monroe Scale groups were statistically significant. In the first phase of the study, 4 patients dropped out (2 on CBZ because of rash and leucopenia; 2 on placebo because of conduction effects on ECG and persisting headaches). Twenty patients agreed to participate in the cross-over experiment, and 14 of these provided either completion or relapse data for phase II. Reasons for the 6 drop outs from this phase of the study included discontinuation for reasons unrelated to medication (n = 1), unsuccessful withdrawal from neuroleptics (n = 2), and CBZ side effects (n = 3). The data from the 14 patients involved in both treatment phases led to the conclusion that CBZ was not effective in the relapse prevention of schizophrenics. The average times before relapse for patients on CBZ and placebo were 22.4 and 44.7 days, respectively, during phase I and 26.0 and 45.6 days during phase II. Whereas 5 of the 14 patients completed the placebo phase without relapse, only 1 was able to complete the CBZ phase. Due to the persuasive nature of these results the authors could not justify continuation of the experiment (originally 68 patients were to be studied). This study indicates that CBZ monotherapy is not an adequate treatment for chronic schizophrenia.

DISCUSSION

The mechanism by which CBZ affects schizophrenic symptoms is still undetermined. Several studies have examined the effects of CBZ on brain neurotransmitters, especially noradrenaline, GABA, dopamine and serotonin, but the results are divergent and often contradictory. There are suggestions that the antipsychotic effects of CBZ might result from a reduction of noradrenaline and dopamine turnover (Post et al 1986), from a reduction of dopaminergic transmission in the brain (Waldmeier 1987), or from an effect on GABA or adenosine receptor systems (Bernasconi 1982; Skeritt et al 1982; 1983). A possible explanation for

the CBZ-associated improvement of negative symptoms might be the decrease in neuroleptic plasma levels (Linnoila et al 1980; Jann et al 1985; Kidron et al 1985; Fast et al 1986; Dose et al 1986; 1987; Kahn et al 1990). Several studies have reported decreased neuroleptic side effects following administration of CBZ (Arana et al 1986; Dose et al 1987). Other reports addressing findings indicating a worsening of schizophrenic symptomatology under a combined treatment with CBZ and neuroleptics suggest this effect may result from a decrease of neuroleptic plasma levels (Pupeschi et al 1991; Kahn et al 1990; Arana et al 1986; Kanter et al 1984; Yerevanian and Hodgman 1985).

The ameliorating influence of CBZ on overactivity, aggression or poor impulse control may contribute to its effects on schizophreniform psychoses, especially those with aggressive outbursts (Neppe 1982; Hakola and Laulumaa 1982; 1984; Luchins 1981, 1983a; 1983b; 1984), overactivity (Reid et al 1981; Gardner and Cowdry 1986b) and with other affective symptoms (Takezaki and Hanaoka 1971; Placidi et al 1986).

Although there are studies testing the efficacy of CBZ as a monotherapeutic agent after the withdrawal of neuroleptics (Sramek et al 1988; Carpenter et al 1991), more commonly CBZ has been added to preexisting neuroleptic therapy (Raju 1984; Tsuneizumi et al 1986; Dose et al 1987; Schulz et al 1989; Mair et al 1990; Kunovac et al 1991; Meszaros et al 1990b; 1990c) — particularly in studies dealing with chronic schizophrenics (Herrera et al 1987a; 1987b; Wetterling 1987; Meszaros et al 1991b; 1991c). In some experiments CBZ has been shown to be useful in the improvement of schizophrenic negative symptoms especially in anhedonia or social retreatment (Hakola and Laulumaa 1982; Klein et al 1984; Ballenger and Post 1984; Herrera et al 1987a; 1987b; Sramek et al 1988; Okuma et al 1989). Perhaps, as suggested, CBZ should be used more on the basis of symptoms than diagnosis (Elphick 1989b).

The administration of CBZ, either adjunctively with neuroleptic treatment or as a monotherapeutic agent, is often associated with the improvement of positive and negative symptoms in schizophrenic and schizoaffective disorders. However, the basis for these positive symptomatic changes remains unclear. The evidence reviewed suggests several possibilities for the results, among which are direct effects of CBZ, benefits accruing from the reduction of affective symptoms, reduction of neuroleptic plasma levels — including the reduction in neuroleptic side effects, or regulation of limbic activity ("antikindling effect"; Post and Kopanda 1976; Post 1990; Ballenger and Post 1978; Pinel 1981).

There are a variety of methodological problems and conceptual considerations which make it difficult to draw conclusions from this review; for example:

1. there is general absence of the use of standardized diagnostic instruments and rating scales — with global effects sometimes based simply on clinicians' impressions;
2. patient groups are heterogeneous — different subtypes of schizophrenia and related psychoses were often investigated within one experiment, and potentially confounding organic factors were not clearly ruled out;
3. the duration of exposure to CBZ differs from study to study, so that no common pharmacological strategy for its use in schizophrenia and schizoaffective disorders can be proposed; hence it follows that no clear onset of a CBZ-related effect can be determined;
4. concurrent medication differs across studies, making it difficult to interpret the basis for treatment outcome;
5. lack of control groups does not allow clear interpretation regarding the basis for the observed effects on psychopathology, i.e., to what extent are the central effects of CBZ influenced by the expectations of patients or raters?
6. Finally, in most studies showing clinical improvement under the augmentation or substitution of CBZ, it remains unclear whether patients benefited from:
   - — a primary antipsychotic effect of CBZ;
   - — a primary psychotropic — anxiolytic effect of CBZ;
   - — improvement of mainly affective and emotional symptoms;
   - — decreased neuroleptic plasma levels (reduction of side effects associated with CBZ administration, especially in haloperidol treated patients);
   - — a reduction of concurrent medication (especially neuroleptics, hypnotics or anticholinergics); or,
   - — a reduction of extrapyramidal side effects caused directly by CBZ, by the reduction of neuroleptics, by the reduction of neuroleptic plasma levels, or by reduction of additional medication.

In most of the controlled studies, clinical improvement in the placebo group was observed. This effect may be due in part to the restrictive study design which offers a higher frequency of "therapeutic contacts" with patients, improving compliance and perhaps ultimately the symptomatology in schizophrenic outpatients.

This review of the literature, and our own experience derived from 3 years of studying CBZ in affective and schizophrenic disorders under controlled conditions, suggest that clinicians should consider the use of CBZ only in addition to neuroleptic treatment when the clinical picture is predominately characterized by any of the following features:

- — violent outbursts, overactivity or poor impulse control;
- — excitement;
- — neuroleptic therapy resistance with concurrent medication;
- — affective symptoms (depression, lability of mood, tension, excitement, anxiety) with or without episodic appearance;
- — positive symptoms combined with affective symptoms;
- — negative symptomatology (blunted affect, anhedonia, social withdrawal);
- — EEG (temporal lobe) abnormalities or symptoms suggesting epileptic aura;
- — history of organic brain disorder, CNS trauma or neurological soft signs; or
- — history of alcohol or drug abuse.

Despite the promising results from various studies there remains a need for further controlled investigations. In these studies, the dosage and plasma levels of CBZ and as well the dosage of basic neuroleptic treatment and additional medication must be standardized. There should be clear diagnostic groups used without EEG abnormalities and without signs of organic brain syndrome or somatic disease. The recording of possible effects of CBZ should be done with standardized rating scales that can measure changes in psychopathology in a detailed way (positive, negative, affective symptoms; side effects of neuroleptic treatment, particularly extrapyramidal side effects and side effects associated with CBZ treatment). Patients should be stabilized on neuroleptics before entering a study. Treatment with CBZ should last at least 6 weeks, with a 2 week follow-up period after withdrawal of CBZ. Regular plasma level measurements of CBZ (not daily dosage because of enzyme induction) and, if possible, neuroleptics should be done to determine pharmacological interactions between the drugs which may occur. Also, follow-up studies are recommended to investigate the stability of improved symptomatology.

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